

REVIEW ARTICLE

Incidence of iatrogenic opioid dependence or abuse in patients with pain who were exposed to opioid analgesic therapy: a systematic review and meta-analysis

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Abstract

Background: The prevalence and incidence of chronic conditions, such as pain and opioid dependence, have implications for policy development, resource allocation, and healthcare delivery. The primary objective of the current review was to estimate the incidence of iatrogenic opioid dependence or abuse after treatment with opioid analgesics.

Methods: Systematic electronic searches utilised six research databases (Embase, Medline, PubMed, Cinahl Plus, Web of Science, OpenGrey). A 'grey' literature search and a reference search of included articles were also undertaken. The PICOS framework was used to develop search strategies and the findings are reported in accordance with the PRISMA Statement.

Results: After eligibility reviews of 6164 articles, 12 studies (involving 310 408 participants) were retained for inclusion in the meta-analyses. A random effects model (DerSimonian-Laird method) generated a pooled incidence of opioid dependence or abuse of 4.7%. There was little within-study risk of bias and no significant publication bias; however, substantial heterogeneity was found among study effects (99.78%). Sensitivity analyses indicated that the diagnostic criteria selected for identifying opioid dependence or abuse (Diagnostic Statistical Manual (DSM-IV) vs International Classification of Diseases (ICD-9)) accounted for 20% and duration of exposure to opioid analgesics accounted for 18% of variance in study effects. Longer-term opioid analgesic exposure, and prescription of strong rather than weak opioids, were associated with a significantly lower incidence of opioid dependence or abuse.

Conclusions: The incidence of iatrogenic opioid dependence or abuse was 4.7% of those prescribed opioids for pain. Further research is required to confirm the potential for our findings to inform prevention of this serious adverse event.

Keywords: analgesics; opioid; incidence; opioid-related disorders; pain

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Editor's key points

- The authors reviewed the literature regarding opioid dependence/abuse after therapeutic analgesic opioid therapy, and performed meta-analysis of the data, which were drawn from more than 300 000 subjects.
- They found an incidence of dependence/abuse of just under 5% after opioid analgesic therapy.
- The incidence appeared lower in patients receiving strong opioids, and in those receiving longer-term exposure. The authors explore explanations for this counter-intuitive finding.

Rationale

The prevalence and incidence of chronic, relapsing conditions, such as chronic pain, have implications for policy development, resource allocation, and healthcare delivery. Physical dependence and addiction are major clinical concerns that may deter adequate analgesic prescribing for patients whose previous treatment regimens have proved unsuccessful. Abuse and diversion of these drugs is an increasing problem that has been associated with increased prescribing rates¹; however, there is little robust scientific evidence concerning the incidence of iatrogenic dependence disorders associated with opioid analgesic therapy. Indeed, there is growing interest² in the phenomenon of 'pseudoaddiction', an 'iatrogenic syndrome that mimics the behavioural symptoms of addiction' in patients receiving inadequate analgesia.³ This growing interest was highlighted in a systematic review examining the 'footprint' of pseudoaddiction in the literature²; however, it concluded that, to date, there is insufficient evidence to support or refute the existence of this phenomenon.

As the current review highlights, there is a dearth of prospective data examining *de novo* incidence of opioid misuse after analgesic prescribing; however, this issue has been examined retrospectively.^{4,5} These studies are limited, however, by an inability to establish the relative onset of chronic pain and opioid dependence. Patients are likely to seek analgesic treatment at an early stage in the development of pain, because it is perceived as problematic immediately after onset. Treatment for opioid dependence, however, is likely to be sought at a relatively later stage in disease development, because it is often not perceived as 'problematic' until symptoms become unmanageable. Additional issues arise because of the vague, and frequently changing, definitions associated with terms such as 'addiction'—a ubiquitous term in the literature which has been used synonymously with 'dependence' or with the wider definition of 'abuse', or, synonymously as an umbrella term, with 'aberrant drug-related behaviour'.

Several reviews have examined the relationship between opioid analgesic prescribing and opioid misuse^{6–10}; however, many examined prevalence (existing cases)—rather than incidence (new cases)—and, in consequence, were unable to conclude that dependence or abuse was a direct function of opioid analgesic treatment. Furthermore, as studies included in many of these reviews were unable to control for pre-trial substance misuse, findings may reflect prevalence—rather than incidence—and, therefore, may not reflect a truly iatrogenic phenomenon.

Whilst the physiological characteristics of acute dependence are anticipated after prolonged exposure to opioids,

clinical diagnoses of opioid dependence or abuse disorders are not. Acute tolerance is demonstrated to occur several minutes or hours after exposure¹¹; however, dependence associated with prolonged exposure has not been characterised. Some studies have suggested that the proposed 7 days¹² has not been challenged adequately and remains a valid threshold,¹³ whilst other studies have used a more cautious approach to ensure that there is no controversy—for example, 2 weeks,¹⁴ 1 month,⁸ or 3 months.¹⁵

The development of addiction-related problems is influenced by numerous factors and, as such, cannot be considered to be a direct function solely of opioid prescribing; however, the iatrogenic component is of key concern to both policy-makers and practitioners. Whilst it is important to acknowledge that a number of reviews have examined this topic, as recently as 2015, their translational value has been restricted by two important limitations. First, a wide range of addiction-related outcomes have been addressed without their having been defined clearly in these reviews, in included articles, or both. This limits the potential for pooling homogenous study findings. Secondly, addressing prevalence (existing cases)—rather than incidence (new cases)—prevents control of pre-existing addiction-related problems. Such an examination of prevalence would, therefore, result in the inclusion of participants whose pre-existing drug-seeking behaviour led them to seek opioid analgesic treatment. Whilst information concerning the prevalence of addiction-related problems in patients in receipt of opioid analgesics is relevant, in terms of resource allocation, it does not permit elucidation on opioid dependence or abuse as an iatrogenic syndrome. The present review is distinguished from previous reviews in that it: (1) focuses on clinically-diagnostic opioid dependence or abuse as the outcome, rather than on a poorly-defined range of addiction-related terminology; and (2) examines incidence (new cases)—rather than prevalence (existing cases)—of opioid dependence or abuse after analgesic treatment, thereby facilitating an understanding of the contributory role of opioid analgesic prescribing on the subsequent development of dependence and abuse disorders.

Objective

The primary objective of the current review was to generate a pooled estimate of the incidence of iatrogenic opioid dependence or abuse in patients with pain who were exposed to opioid analgesic therapy, based on a systematic review of published studies. It was hoped that data concerning dependence and abuse would be provided separately; however, it was anticipated that this distinction probably could not be made in studies. In the absence of distinct data for these two disorders, it was decided that data for these disorders would be pooled to provide an indication of a clinical dependence/abuse disorder. Should substantial heterogeneity be identified, sensitivity analyses would be undertaken in an effort to describe variance in study effects.

Methods

The established Population, Interventions, Comparators, Outcomes and Study design (PICOS) framework was used to design the review and to develop an appropriate search strategy. The findings are reported in accordance with the recommendations set out in the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA)¹⁶. The

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